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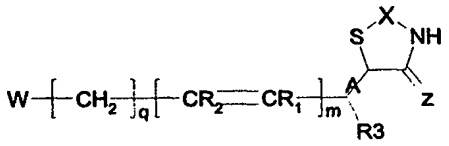
(54) Title: RHODANINE DERIVATIVES FOR THE TREATMENT AND PREVENTION OF METABOLIC BONE DISORDERS



(I)

(57) Abstract

The object of the present invention are compounds of general formula (I), in which m signifies a number between 0 and 8; q signifies a number between 0 and 8; X signifies the group CH_2 or C=S, whereby A signifies a single bond and m signifies 0 when X signifies CH_2; A signifies a single or double bond; R_1, R_2 signify hydrogen or lower alkyl, whereby R_1 and R_2 can be the same or different and, when m signifies 2–8, R_1 and R_2 in the group CR_1=CR_2 can have various significances within the following sequence; R_3 signifies hydrogen or lower alkyl; Z signifies oxygen, sulphur; W signifies an optionally mono– or polysubstituted saturated or unsaturated mono–, bi– or tricycle which can contain one or more hetero atoms, as well as their physiologically compatible salts, esters, optically active forms, racemates, tautomers, as well as derivatives which can be metabolized *in vivo* to compounds of general formula (I), as well as the use of these compounds for the production of medicaments for the prophylaxis or therapy of metabolic bone disorders.

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Rhodanine derivatives for the treatment and prevention of metabolic bone disorders

The present invention is concerned with rhodanine derivatives for the treatment and prevention of metabolic bone disorders, a process for their manufacture as well as medicaments which contain these compounds.

In healthy persons the synthesis and degradation processes in bones is almost in equilibrium, i.e. the activity of the osteoblasts and osteoclasts is balanced. However, if this equilibrium is disturbed in favour of the osteoclasts and/or to the detriment of the osteoblasts, this leads to a reduction in the bone mass and to a negative change in the bone structure and function.

Hitherto, bone resorption inhibitors such as oestrogens, calcitonin and biphosphonates have primarily been used for the treatment of metabolic bone disorders. The use of these substances is, however, limited and also does not show the desired effect in all cases. Compounds which have a stimulating activity on bone synthesis and in addition contribute to an increase in an already reduced bone mass are accordingly of especial significance for the treatment of metabolic bone disorders.

Compounds having the rhodanine structural element are known as antidiabetics, cytostatics, inflammation inhibitors and for the treatment of cardiovascular illnesses, e.g. WO9305039, WO 9705875, EP 677517.

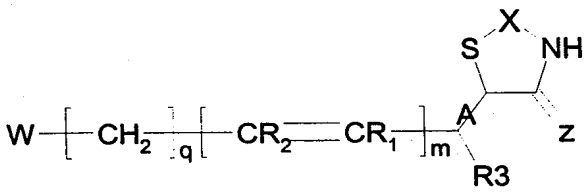
The parathyroid hormone (PTH), a hormone from the parathyroid gland, is the natural ligand of the receptor and an important regulator for the maintenance of the calcium level in the body. PTH can stimulate bone formation or bone resorption. In this, it acts as a regulatory hormone on a series of enzymes, inter alia, on adenylate cyclase (cAMP synthesis) and on ornithine decarboxylase. PTH mobilizes calcium from bones in the case of calcium deficiency, reduces calcium excretion from the kidneys and simultaneously improves the resorption of calcium from the intestine by an increased synthesis of 1,25-$(OH)_2D_3$. A normalization of the calcium level is achieved by the

action on these target organs. On the other hand, the incorporation of calcium in bones is stimulated in the case of an elevated calcium level. This osteoanabolic activity of PTH and its fragments has been attributed to the activation of adenylate cyclase and of cAMP-dependent protein kinases (Rixon, R. Whitfield, J. et al JMBR 9 (8) 1179-89 (1994).

Surprisingly, it has now been found that rhodanine derivatives of the present invention stimulate the PTH receptor-mediated cAMP formation. Compounds of the present invention are accordingly suitable for the broad treatment of metabolic bone disorders. They can be used primarily to good effect where the bone synthesis is disturbed, i.e. they are especially suitable for the treatment of osteopenic disorders of the skeletal system such as e.g. osteoporosis, inter alia, osteogenesis imperfecta as well as for the local assistance in bone regeneration and osteoinduction such as e.g. in orthopedic and maxillary medical indications, in fracture healing, osteosyntheses, pseudoarthroses and for the healing in of bone implants. However, having regard to these properties they also find use in the prophylaxis of osteoporosis.

By their influence on bone metabolism medicaments with the rhodanine derivatives of the present invention as active substances furthermore form a basis for the local and systemic treatment of rheumatoid arthritis, osteoarthritis and degenerative arthrosis.

The object of the present invention are compounds of general formula (I),



(I)

in which

m signifies a number between 0 and 8,

q signifies a number between 0 and 8

X signifies the group CH_2 or C=S, whereby A signifies a single bond and m signifies 0 when X signifies CH_2,

A signifies a single or double bond

R_1, R_2 signify hydrogen or lower alkyl, whereby R_1 and R_2 can be the same or different and, when m signifies 2-8, R_1 and R_2 in the group $CR_1=CR_2$ can have various significances within the following sequence

R_3 signifies hydrogen or lower alkyl

Z signifies oxygen, sulphur

W signifies an optionally mono- or polysubstituted saturated or unsaturated mono- (sic), bi- or tricycle which can contain one or more hetero atoms,

As a rule, lower alkyl signifies linear or branched alkyl residues with one to six carbon atoms, preferably methyl, ethyl, propyl, i-propyl, butyl, t-butyl, pentyl, hexyl, particularly methyl.

Alkoxy groups signify a combination of a C_1-C_{10}-alkyl group in accordance with the above definition with an oxygen atom, e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy and pentoxy groups.

Under monocycle there are to be understood optionally mono- or polysubstituted saturated or unsaturated ring systems with 3-8, preferably 5-7 carbon atoms, which optionally can be interrupted by one or more hetero atoms, such as nitrogen, oxygen or sulphur, especially the phenyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, morpholinyl, thiamorpholinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, furyl, thiophenyl, imidazolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl or 1,2,4-triazolyl residue, as well as residues such as e.g. phenyl phenyl ether, diphenylmethane and biphenyl. Substituents are preferably lower alkyl, alkoxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, benzyl, benzyloxy, phenyl, dioxymethylene, cyanobenzoxymethyl, pyrrolidine, alkoxyhydroxy, carboxyl, dialkylamino, styryl and halogen.

In the case of the bicycle set forth under W, this is preferably a residue such as the naphthyl, tetrahydronaphthyl, decalinyl, quinolinyl, chromane, chromene, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, indolyl, benzimidazolyl, indazolyl, oxindolyl, benzofuranyl, benzothiophenyl, benzothiazolyl, benzoxazolyl or purinyl residue, especially the indolyl, naphthyl, benzimidazolyl, quinolinyl, tetrahydroquinolinyl, benzothiophenyl and benzofuranyl residue, which optionally can

be mono- or polysubstituted. Substituents are preferably lower alkyl, C_1-C_6-alkoxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, benzyl, benzyloxy, phenyl, dioxymethylene, cyanobenzoxymethyl, pyrrolidine, alkoxyhydroxy, carboxyl, dialkylamino, styryl and halogen.

Tricycle signifies anthracene, fluorene, dibenzofuran, dibenzooxepine or carbazole.

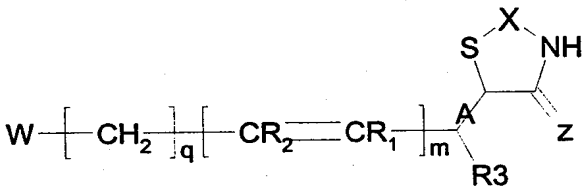
Compounds of formula I, wherein W is phenyl, naphthyl, indolyl or thienyl, XnC = S, Z = oxygen and m and g are both 0, are disclosed in EP-A-0677517 and WO-A-96/26207, however for the treatment of Alzheimer's disease or as hypoglycemic agents.

Compounds of formula I, wherein W is phenyl, furyl, thienyl or pyrrolyl, X is C = S, Z is oxygen, A is a double bond and m is 0 or 1 and g is unequal 0 or n is unequal 0 and g is 2 are disclosed in EP-A-0398179, however as aldose reductase inhibitor.

Compounds of formula I, wherein W is endolyl, X is C = S, Z is oxygen, A is a double bond and m is 1 and g is 0 is disclosed in WO-A-98/01445, however as ATP-ase inhibitors.

Compounds formula I, wherein W is 4-(2,5-di-tert. butyl-phenol) and X is methylene are disclosed in EP-A-0211670, however for the treatment of inflammations.

Therefore subject of the present invention are also new compounds of formula I



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R_1, R_2 signify hydrogen or lower alkyl, whereby R_1 and R_2 can be the same or different and, when m signifies 2-8, R_1 and R_2 in the group $CR_1=CR_2$ can have various significances within the following sequence

R_3 signifies hydrogen or lower alkyl

Z signifies oxygen, sulphur

W signifies an optionally mono- or polysubstituted saturated or unsaturated mono- (sic), bi- or tricycle which can contain one or more hetero atoms,

whereas W is not phenyl, naphthyl, indolyl or thienly, if X is C = X, Z is sulfur and m and g are both 0,

whereas W is not phenyl, furyl, thienyl or pyrrolyl, if XnC = S, Z is sulfur, A is a double bond and m is 0 or 1 and g is unequal 0 or m is unequal 0 and g is 2,

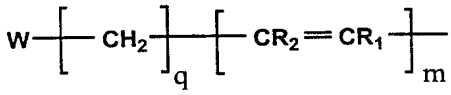
whereas W is not indolyl, if X is C = S, Z is sulfur, A is a double bond and m is 1 and g is 0,

whereas W is not 4-(2.5-di-tert. butyl-phenyl), if X is methylene, as well as their physiologically compatible salts, esters, optically active forms, racemates, tautomers, as

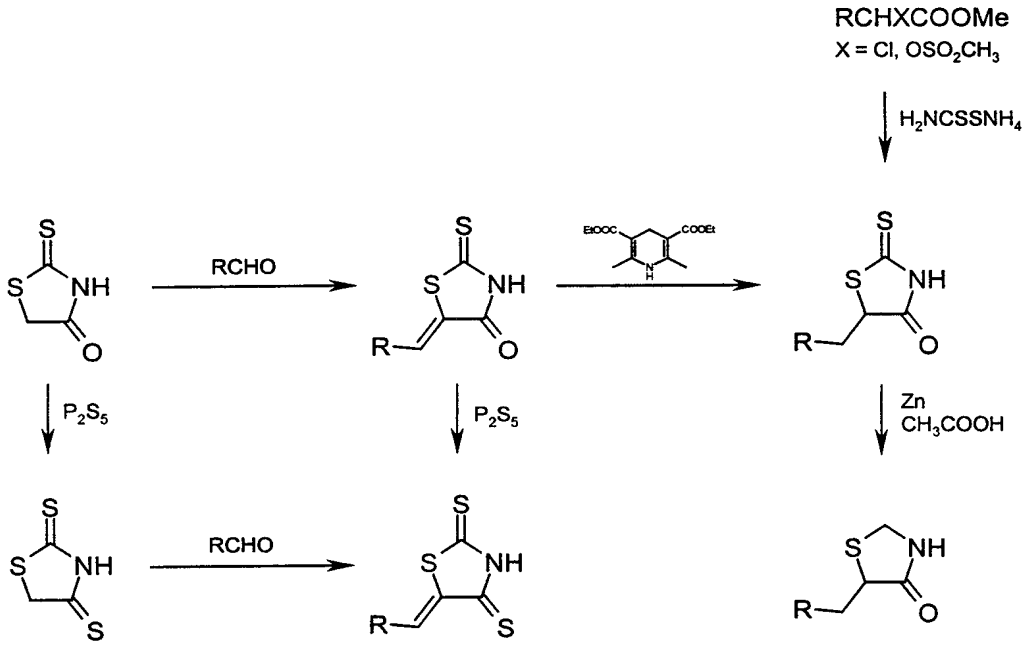
well as derivatives which can be metabolized *in vivo* to compounds of general formula (I), as well as the use of these compounds for the production of medicaments.

Preferred are compounds of general formula I in which X signifies C=S, Z signifies oxygen, A signifies a double bond, m signifies a number from 0 to 2, q signifies 0 or 1, R_1 and R_2 respectively signify hydrogen or methyl, R_3 signifies hydrogen or methyl and W signifies a phenyl, naphthyl, thiophenyl, benzothiophenyl, furanyl, phenyl, pyridyl, cyclohexenyl, dibenzooxepinyl, pyrryl or imidazolyl residue, which optionally can be mono- or polysubstituted by halogen, hydroxy, methoxy, ethoxy, benzyloxy, butoxycarbnyl, methyl, i-propyl, t-butyl, dioxymethylenee, cyanobenzoxymethyl or benzyl.

The manufacture of the compounds of general formula (I) is possible according to methods known per se. An overview of the methods of synthesis is set forth in Scheme 1 (J. Med. Chem. 37 322-8 (1994); Chem. Pharm. Bull. 30 3563-73 (19982); Chem. Heterocycl. Compd. EN 2 267-70 (1996); J. Med. Chem. 21 82-7 (1978); J. Org. Chem. 57 4047-49 (1992); T.L. 35 6971-74 (1994)); R signifies the group:



Scheme 1



The α-halocarboxylic acids and aldehydes used as starting materials are either commercially available, known or can be prepared analogously to the generally known processes.

Compounds of formula (I) can be administered (sic) in liquid, solid or aerosol form orally, enterally, parenterally, topically, nasally, pulmonary or rectally in all usual non-toxic pharmaceutically acceptable carrier materials, adjuvants and additives. The compounds of formula (I) can also be applied locally to/in the bones (optionally with surgical intervention). The term parenteral embraces subcutaneous, intravenous and intramuscular delivery or infusions. Oral administration forms can be e.g. tablets, capsules, dragees, syrups, solutions, suspensions, emulsions, elixirs etc., which can contain one or more additives from the following groups, such as flavourings, sweeteners, colouring agents and preservatives. Oral administration forms contain the active ingredient together with non-toxic, pharmaceutically acceptable carrier materials which are suitable for the production of tablets, capsules, dragees etc., such as e.g. calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate;

starch, mannitol, methylcellulose, talc, highly dispersible silicic acids, high molecular fatty acids (such as stearic acid), groundnut oil, olive oil, paraffin, miglyol, gelatine, agar-agar, magnesium stearate, beeswax, cetyl alcohol, lecithin, glycerol, animal and vegetable fats, solid high molecular polymers (such as polyethylene glycol). Tablets, capsules, dragees etc. can be provided with an appropriate coating, e.g. glyceryl monostearate or glyceryl distearate, in order to prevent undesired side effects in the gastrointestinal tract or to give a longer duration of action by the delayed absorption in the gastrointestinal tract. As the injection medium there are preferably used sterile injectable aqueous or oily solutions or suspensions which contain the usual additives such as stabilizers and solubilizers. Such additives can be e.g. water, isotonic saline, 1,3-butanediol, fatty acids (such as oleic acid), mono- and diglycerides or miglyol. For rectal use there can be used all suitable non-irritating additives which are solid at normal temperatures and liquid at rectal temperatures, such as e.g. cocoa butter and polyethylene glycol. Pharmaceutically usual carrier media are used for application as aerosols. Creams, tinctures, gels, solutions or suspensions etc. with the pharmaceutically usual additives are used for external application. The dosage can depend n a variety of factors such as mode of administration, species, age and/or individual condition. The doses to be administered daily or at intervals lie at 1-1000 mg/individual, preferably at 10-250 mg/individual, and can be taken at one time or divided over several times.

The compounds of formula (I) can also be applied locally to/in the bones (optionally with surgical intervention). The application directly to/in the bones (optionally with surgical intervention) can be effected locally or carrier-bonded either in solution or suspension, conveniently by infusion or injection. Carrier-bonded compounds of formula (I) can be administered, for example, as gels, pastes, solids or as a coating on implants.

Biocompatible and preferably biodegradable materials are used as the carrier. Preferably, the materials themselves also induce wound healing or osteogenesis.

For local application it is preferred that the compounds of formula (I) are imbedded in polymer gels or films in order to immobilize them and to apply these preparations directly on the site of the bone to be treated. Such polymer-based gels or films consist, for example, of glycerine, methylcellulose, hyaluronic acid, polyethylene oxides and/or

poloxamers. Also suitable are collagen, gelatines and alginates and are described, for example, in WO 93/00050 and WO 93/20859. Further polymers are polylactic acid (PLA) and copolymers of lactic acid and glycolic acid (PLPG) (Hollinger el al., J. Biomed. Mater. Res. 17 71-82 (1983)) as well as the bone derivative "Demineralized Bone Matrix" (DBM) (Guterman et al. Kollagen Rel. Res. 8 419-4319 (1988). Also suitable are polymers as are used, for example, for the adsorption of TGFβ and which are described in EP-A 0 616 814 and EP-A-0 567 391 and synthetic bone matrices in accordance with WO 91/18558.

Likewise suitable as carriers for the compounds of formula (I) are materials which are usually used for the implantation of bone substitutes or otherwise of therapeutically active substances. Such carriers are based, for example, on calcium sulphate, tricalcium phosphate, hydroxylapatite (sic) and its biodegradable derivatives and polyanhydrides. Apart from these biodegradable carriers there are also suitable carriers which are not biodegradable, but which are biocompatible. Such carriers are, for example, sintered hydroxylapatite, bioglass, aluminates or other ceramic materials (e.g. calcium aluminium phosphate). These materials are preferably used in combination with the biodegradable materials, such as especially polylactic acid, hydroxylapatite, collagen or tricalcium phosphate. Further non-degradable carriers are described, for example, in US Patent 4,164,560.

It is especially preferred to use a carrier which liberates the compounds of formula (I) continuously at the target site. Especially suitable for this are e.g. "slow release pellets" from Innovative Research of America, Toledo, Ohio, USA. Pellets which release the compounds of formula (I) over several days, preferably up to 100 days with a daily dosage of 1-10 mg/kg per day, are especially preferred.

Preferred in the scope of the present invention are, apart form the compounds named in the Examples and compounds derivable by a combination of all of the significances of the substituents set forth in the claims, the following derivatives as well as their physiologically compatible salts, esters, optically active forms, racemates, tautomers as well as derivatives which can be metabolized *in vivo* to compounds of general formula (I), as well as the use of these compounds for the production of medicaments,

Preferred Compounds (PC):

1. 5-(9*H*-Fluoren-2-ylmethylene)-2-thioxo-thiazolidin-4-one
2. 5-Phenanthren-9-ylmethylene-thiazolidine-2,4-dithione
3. 5-Anthracen-9-ylmethyl-2-thioxo-thiazolidin-4-one
4. 5-(5-Furan-2-yl-penta-2,4-dienylidene)-2-thioxo-thiazolidin-4-one
5. 5-(2-Methoxy-benzylidene)-thiazolidine-2,4-dithione
6. 5-(2,3-Dimethoxy-benzyl)-2-thioxo-thiazolidin-4-one
7. 5-[3-(2,4-Dimethoxy-phenyl)-allylidene]-2-thioxo-thiazolidin-4-one
8. 2-Thioxo-5-(2,4,5-trimethoxy-benzylidene)-thiazolidin-4-one
9. 5-(2,4,6-Trimethoxy-benzylidene)-thiazolidine-2,4-dithione
10. 5-(2,5-Dimethoxy-benzyl)-2-thioxo-thiazolidin-4-one
11. 5-[3-(2-Hydroxy-phenyl)-allylidene]-2-thioxo-thiazolidin-4-one
12. 5-(2-Hydroxy-3-methoxy-benzylidene)-2-thioxo-thiazolidin-4-one
13. 5-(3-Ethoxy-2-hydroxy-benzylidene)-thiazolidine-2,4-dithione
14. 5-(2,3-Dihydroxy-benzyl)-2-thioxo-thiazolidin-4-one
15. 5-[3-(4-Diethylamino-2-hydroxy-phenyl)-allylidene]-2-thioxo-thiazolidin-4-one
16. 5-(2-Hydroxy-4-methoxy-benzylidene)-2-thioxo-thiazolidin-4-one
17. 5-(2,4,6-Trihydroxy-benzylidene)-thiazolidine-2,4-dithione
18. 5-(2-Hydroxy-5-methoxy-benzyl)-2-thioxo-thiazolidin-4-one
19. 2-Thioxo-5-(3-*o*-tolyl-allylidene)-thiazolidin-4-one
20. 5-(4-Methoxy-2,3-dimethyl-benzylidene)-2-thioxo-thiazolidin-4-one
21. 5-(2,4,6-Trimethyl-benzylidene)-thiazolidine-2,4-dithione
22. 5-(2,5-Dimethyl-benzyl)-2-thioxo-thiazolidin-4-one
23. 5-{3-[3-(4-Methoxy-phenoxy)-phenyl]-allylidene}-2-thioxo-thiazolidin-4-one
24. 5-[3-(4-*tert*-Butyl-phenoxy)-benzylidene]-2-thioxo-thiazolidin-4-one
25. 5-(3-*p*-Tolyloxy-benzylidene)-thiazolidine-2,4-dithione
26. 5-(3-Methoxy-benzyl)-2-thioxo-thiazolidin-4-one
27. 2-Thioxo-5-[3-(3,4,5-trimethoxy-phenyl)-allylidene]-thiazolidin-4-one
28. 5-(4-Benzyloxy-3-methoxy-benzylidene)-2-thioxo-thiazolidin-4-one
29. 5-(3,5-Dimethoxy-benzylidene)-thiazolidine-2,4-dithione
30. 5-(3-Benzyloxy-benzyl)-2-thioxo-thiazolidin-4-one
31. 5-[3-(3-Hydroxy-4-methoxy-phenyl)-allylidene]-2-thioxo-thiazolidin-4-one
32. 5-(3,4-Dihydroxy-benzylidene)-2-thioxo-thiazolidin-4-one

33. 5-(3-Methyl-benzylidene)-thiazolidine-2,4-dithione
34. 5-(4-Methoxy-3-methyl-benzyl)-2-thioxo-thiazolidin-4-one
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37. 5-(4-Methoxy-benzylidene)-thiazolidine-2,4-dithione
38. 5-(3-Benzyloxy-4-methoxy-benzyl)-2-thioxo-thiazolidin-4-one
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50. 5-(4-Hydroxy-benzyl)-2-thioxo-thiazolidin-4-one
51. 5-[3-(4-Hydroxy-3,5-dimethoxy-phenyl)-allylidene]-2-thioxo-thiazolidin-4-one
52. 5-(3-Ethoxy-4-hydroxy-benzylidene)-2-thioxo-thiazolidin-4-one
53. 5-(4-Hydroxy-3,5-dimethyl-benzylidene)-thiazolidine-2,4-dithione
54. 5-Biphenyl-4-ylmethyl-2-thioxo-thiazolidin-4-one
55. 5-[3-(4-Isopropyl-phenyl)-allylidene]-2-thioxo-thiazolidin-4-one
56. 5-(4-Methyl-benzylidene)-2-thioxo-thiazolidin-4-one
57. 5-(4-Ethyl-benzylidene)-thiazolidine-2,4-dithione
58. 5-(2,2-Diphenyl-ethyl)-2-thioxo-thiazolidin-4-one
59. 5-(2-Pentyl-3-phenyl-allylidene)-2-thioxo-thiazolidin-4-one
60. 5-(2-Hexyl-3-phenyl-allylidene)-thiazolidine-2,4-dithione
61. 5-Phenthyl-2-thioxo-thiazolidin-4-one
62. 5-(5-Phenyl-penta-2,4-dienylidene)-2-thioxo-thiazolidin-4-one
63. 5-[3-(2-Methoxy-phenyl)-allylidene]-2-thioxo-thiazolidin-4-one
64. 5-[3-(4-Dimethylamino-phenyl)-allylidene]-thiazolidine-2,4-dithione
65. 5-(3-Phenyl-propyl)-2-thioxo-thiazolidin-4-one
66. 5-[3-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-allylidene]-2-thioxo-thiazolidin-4-one
67. 5-(3-Ethoxy-4-methoxy-benzylidene)-2-thioxo-thiazolidin-4-one

68. 5-(4-Diethoxymethyl-benzylidene)-thiazolidine-2,4-dithione
69. 5-(4-Dimethylamino-naphthalen-1-ylmethyl)-2-thioxo-thiazolidin-4-one
70. 5-[3-(2,6-Dimethoxy-phenyl)-allylidene]-2-thioxo-thiazolidin-4-one
71. 5-(2,4-Dimethoxy-3-methyl-benzylidene)-2-thioxo-thiazolidin-4-one
72. 5-(4-Styryl-benzylidene)-thiazolidine-2,4-dithione
73. 5-[4-(3-Dimethylamino-propoxy)-benzyl]-2-thioxo-thiazolidin-4-one
74. 5-[3-(2-Methyl-1*H*-indol-3-yl)-allylidene]-2-thioxo-thiazolidin-4-one
75. 5-(4-Hydroxy-3-methyl-benzylidene)-2-thioxo-thiazolidin-4-one
76. 5-(2-Allyloxy-benzylidene)-thiazolidine-2,4-dithione
77. 5-(2-Hexyloxy-benzyl)-2-thioxo-thiazolidin-4-one
78. 5-[3-(4-Propoxy-phenyl)-allylidene]-2-thioxo-thiazolidin-4-one
79. 5-(4-Pentyloxy-benzylidene)-2-thioxo-thiazolidin-4-one
80. 5-(4-Octyloxy-benzylidene)-thiazolidine-2,4-dithione
81. 5-(5-Benzyloxy-1*H*-indol-3-ylmethyl)-2-thioxo-thiazolidin-4-one
82. 5-(3-Benzofuran-2-yl-allylidene)-2-thioxo-thiazolidin-4-one
83. 5-(4-Pyrrolidin-1-yl-benzylidene)-2-thioxo-thiazolidin-4-one
84. 5-(2,3,4,5,6-Pentamethyl-benzylidene)-thiazolidine-2,4-dithione
85. 5-(2-Benzyloxy-benzyl)-2-thioxo-thiazolidin-4-one
86. 5-[3-(3-Ethoxy-phenyl)-allylidene]-2-thioxo-thiazolidin-4-one
87. 5-(3,4-Dihydroxy-5-methoxy-benzylidene)-thiazolidine-2,4-dithione
88. 5-(3,5-Dihydroxy-benzyl)-2-thioxo-thiazolidin-4-one
89. 5-[3-(4-Ethoxy-3-methoxy-phenyl)-allylidene]-2-thioxo-thiazolidin-4-one
90. 5-(4-Hexyloxy-benzylidene)-2-thioxo-thiazolidin-4-one
91. 5-(4-Heptyloxy-benzylidene)-thiazolidine-2,4-dithione
92. 5-(7-Methoxy-benzo[1,3]dioxol-5-ylmethyl)-2-thioxo-thiazolidin-4-one
93. 5-[5-(4-Methoxy-phenyl)-penta-2,4-dienylidene]-2-thioxo-thiazolidin-4-one
94. 2-Thioxo-5-(2,4,5-trimethyl-benzylidene)-thiazolidin-4-one
95. 5-(4-Decyloxy-benzyliden)-thiazolidine-2,4-dithione
96. 5-[3-(2-*tert*-Butylsulphanyl-phenyl)-allylidene]-2-thioxo-thiazolidin-4-one
97. 5-(4-Butyl-benzylidene)-2-thioxo-thiazolidin-4-one
98. 5-(2-Hydroxy-3-methyl-benzylidene)-thiazolidine-2,4-dithione
99. 5-(4-*tert*-Butoxy-benzyl)-2-thioxo-thiazolidin-4-one
100. 5-[3-(4-Hexyl-phenyl)-allylidene]-2-thioxo-thiazolidin-4-one
101. 5-(4-Octyl-benzylidene)-2-thioxo-thiazolidin-4-one
102. 5-(4-Dodecyloxy-benzylidene)-thiazolidine-2,4-dithione

103. 5-(4-Pentyl-benzyl)-2-thioxo-thiazolidin-4-one
104. 5-[3-(3-Amino-phenyl)-allylidene]-2-thioxo-thiazolidin-4-one
105. 5-(2-Ethoxy-naphthalen-1-ylmethylene)-2-thioxo-thiazolidin-4-one
106. 5-(7-Methyl-1*H*-indol-3-ylmethylene)-thiazolidine-2,4-dithione
107. 5-[3-(3,5-Dimethyl-1-phenyl-1*H*-pyrazol-4-yl)-allylidene]-2-thioxo-thiazolidin-4-one
108. 5-(2,5-Dimethyl-1-phenyl-1*H*-pyrrol-3-ylmethylene)-2-thioxo-thiazolidin-4-one
109. 5-[3-(2,2-Dimethyl-chroman-6-yl)-allylidene]-2-thioxo-thiazolidin-4-one
110. 5-(4-Isopropoxy-benzylidene)-2-thioxo-thiazolidin-4-one
111. 5-(4-Hydroxy-naphthalen-1-ylmethyl)-2-thioxo-thiazolidin-4-one
112. 5-(5-Furan-2-yl-4-methyl-penta-2,4-dienylidene)-2-thioxo-thiazolidin-4-one
113. 5-(2,3-Dihydro-benzofuran-5-ylmethylene)-thiazolidine-2,4-dithione
114. 5-Quinolin-2-ylmethyl-2-thioxo-thiazolidin-4-one
115. 5-[3-(4-Dibutylamino-phenyl)-allylidene]-2-thioxo-thiazolidin-4-one
116. 5-(4-Isobutyl-benzylidene)-2-thioxo-thiazolidin-4-one
117. 5-[3-(4-Hydroxy-3-methoxy-phenyl)-allylidene]-thiazolidine-2,4-dithione
118. 5-(6-Methoxy-naphthalen-2-ylmethyl)-2-thioxo-thiazolidin-4-one
119. 5-[3-(1-Hydroxy-naphthalen-2-yl)-allylidene]-2-thioxo-thiazolidin-4-one
120. 5-(2-Methyl-4-phenyl-pentylidene)-thiazolidine-2,4-dithione
121. 5-[3-(4-Octadecyloxy-phenyl)-allylidene]-2-thioxo-thiazolidin-4-one
122. 5-(4-Diphenylamino-benzylidene)-2-thioxo-thiazolidin-4-one
123. 5-(3,4,5-Trihydroxy-benzylidene)-thiazolidine-2,4-dithione
124. 5-(4-Dimethylamino-2-methoxy-benzyl)-2-thioxo-thiazolidin-4-one
125. 5-[3-(2-Benzyloxy-4,5-dimethoxy-phenyl)-allylidene]-2-thioxo-thiazolidin-4-one
126. 5-[3-(2-Hydroxy-ethoxy)-benzylidene]-2-thioxo-thiazolidin-4-one
127. 5-[2-(2-Hydroxy-ethoxy)-benzylidene]-thiazolidine-2,4-dithione
128. 5-[4-(2-Hydroxy-ethoxy)-benzyl]-2-thioxo-thiazolidin-4-one
129. Carboxylic acid *tert*-butyl ester 2-methoxy-4-[3-(4-oxo-2-thioxo-thiazolidin-5-ylidene)-propenyl]-phenyl ester
130. 5-(3,5-Di-*tert*-butyl-2-hydroxy-benzylidene)-2-thioxo-thiazolidin-4-one
131. 5-(2,4-Diethoxy-3-methyl-benzylidene)-thiazolidine-2,4-dithione
132. 5-[3-(4-Methanesulphonyl-phenyl)-allylidene]-2-thioxo-thiazolidin-4-one
133. 5-(2-Hydroxy-5-methyl-benzylidene)-2-thioxo-thiazolidin-4-one
134. 5-Benzo[*b*]thiophen-2-ylmethylene-thiazolidine-2,4-dithione
135. 5-(5-Benzo[*b*]thiophen-2-yl-penta-2,4-dienylidene)-2-thioxo-thiazolidin-4-one

136. 5-(3-Naphthalen-2-yl-allylidene)-thiazolidine-2,4-dithione
137. 2-Thioxo-5-[3-(2,6,6-trimethyl-cyclohex-1-enyl)-allylidene]-thiazolidin-4-one
138. 5-(3-*tert*-Butyl-4-hydroxy-benzylidene)-2-thioxo-thiazolidin-4-one
139. 5-(2,4-Bis-benzyloxy-benzylidene)-thiazolidine-2,4-dithione
140. 5-(4-Benzyl-benzyl)-2-thioxo-thiazolidin-4-one
141. 5-[3-(1*H*-Pyrrol-2-yl)-allylidene]-2-thioxo-thiazolidin-4-one
142. 5-(5,6-Diethoxy-benzo[*b*]thiophen-2-ylmethylene)-thiazolidine-2,4-dithione
143. 5-[3-(1-Methyl-1*H*-pyrrol-3-yl)-allylidene]-2-thioxo-thiazolidin-4-one
144. 5-Cyclohexylmethylene-2-thioxo-thiazolidin-4-one
145. 5-(2-Hydroxy-4,6-dimethoxy-benzylidene)-2-thioxo-thiazolidin-4-one
146. 5-(4-Benzyloxy-2-hydroxy-benzylidene)-thiazolidine-2,4-dithione
147. 5-(5-Benzyloxy-2-hydroxy-benzyl)-2-thioxo-thiazolidin-4-one
148. 5-{3-[4-(Benzo[1,3]dioxol-5-ylmethoxy)-phenyl]-allylidene}-2-thioxo-thiazolidin-4-one
149. 5-(4-Benzyloxy-3,5-dimethoxy-benzylidene)-2-thioxo-thiazolidin-4-one
150. 5-(4-Benzyloxy-3,5-dihydroxy-benzylidene)-thiazolidine-2,4-dithione
151. 5-(2,5-Bis-benzyloxy-benzyl)-2-thioxo-thiazolidin-4-one
152. 5-[3-Methyl-5-(2,6,6-trimethyl-cyclohex-1-enyl)-penta-2,4-dienylidene]-thiazolidine-2,4-dithione
153. 2-(2,4-Dithioxo-thiazolidin-5-ylidenemethyl)-benzoic acid
154. 2-Methoxy-4-(4-oxo-2-thioxo-thiazolidin-5-ylmethyl)-phenyl acetate
155. 2-Hydroxy-5-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-benzoic acid
156. 4-(2,4-Dithioxo-thiazolidin-5-ylidenemethyl)-benzoic acid
157. 3-[4-(4-Oxo-2-thioxo-thiazolidin-5-ylmethyl)-phenyl]-acrylic acid
158. 3-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-phenyl acetate
159. [4-(2,4-Dithioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-acetic acid
160. 3-(4-Oxo-2-thioxo-thiazolidin-5-ylmethyl)-benzoic acid
161. 5-(5,7-Dimethyl-4-oxo-4*H*-chromen-3-ylmethylene)-2-thioxo-thiazolidin-4-one
162. 11-(2,4-Dithioxo-thiazolidin-5-ylidenemethyl)-1,4-dihydroxy-10-methoxy-5,8-dimethyl-1*H*-benzo[*e*]furo[3',4':3,4]benzo[*b*][1,4]dioxepine-3,7-dione
163. 8-(4-Oxo-2-thioxo-thiazolidin-5-ylmethyl)-naphthalene-1-carboxylic acid
164. 2-Acetoxy-5-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-phenyl acetate
165. 2-Amino-3-(2,4-dithioxo-thiazolidin-5-ylidenemethyl)-6,7-dimethyl-chromen-4-one
166. 5-(6-Ethyl-4-oxo-4*H*-chromen-3-ylmethyl)-2-thioxo-thiazolidin-4-one

167. 5-(6,8-Dimethyl-4-oxo-4*H*-chromen-3-ylmethylene)-2-thioxo-thiazolidin-4-one
168. Methyl 2-(2,4-dithioxo-thiazolidin-5-ylidenemethyl)-benzoate
169. Methyl 3-(4-oxo-2-thioxo-thiazolidin-5-ylmethyl)-1*H*-indole-6-carboxylate
170. 5-(1-*p*-Tolyl-ethylidene)-thiazolidine-2,4-dithione
171. 5-[1-(4-Methoxy-phenyl)-ethyl]-2-thioxo-thiazolidin-4-one
172. 5-[1-(3,5-Dihydroxy-phenyl)-ethylidene]-thiazolidine-2,4-dithione
173. 2,6-Diacetoxy-4-(4-oxo-2-thioxo-thiazolidin-5-ylmethyl)-phenyl acetate
174. 5-(3-Cyclohexyl-allylidene)-2-thioxo-thiazolidin-4-one
175. 5-[5-(3,4-Diethoxy-2,5-dimethyl-phenyl)-penta-2,4-dienylidene]-2-thioxo-thiazolidin-4-one
176. 2-Hydroxy-5-[3-(4-oxo-2-thioxo-thiazolidin-5-ylidene)-propenyl]-benzoic acid
177. 3-[3-(4-Oxo-2-thioxo-thiazolidin-5-ylidene)-propenyl]-phenyl acetate
178. 5-[3-(5,7-Dimethyl-4-oxo-4*H*-chromen-3-yl)-allylidene]-2-thioxo-thiazolidin-4-one
179. 2-Acetoxy-5-[3-(4-oxo-2-thioxo-thiazolidin-5-ylidene)-propenyl]-phenyl acetate
180. 5-[3-(6,8-Dimethyl-4-oxo-4*H*-chromen-3-yl)-allylidene]-2-thioxo-thiazolidin-4-one
181. 5-(3-Phenyl-but-2-enylidene)-2-thioxo-thiazolidin-4-one
182. 5-(3-Thiophen-2-yl-but-2-enylidene)-2-thioxo-thiazolidin-4-one
183. 5-(2,4-Dimethoxy-benzyl)-thiazolidin-4-one
184. 5-(2-Hydroxy-benzyl)-thiazolidin-4-one
185. 5-(4-Diethylamino-2-hydroxy-benzyl)-thiazolidin-4-one
186. 5-(2-Methyl-benzyl)-thiazolidin-4-one
187. 5-[3-(4-Methoxy-phenoxy)-benzyl]-thiazolidin-4-one
188. 5-(3,4,5-Trimethoxy-benzyl)-thiazolidin-4-one
189. 5-(3-Hydroxy-4-methoxy-benzyl)-thiazolidin-4-one
190. 5-(4-Diethylamino-benzyl)-thiazolidin-4-one
191. 5-(4-Ethoxy-benzyl)-thiazolidin-4-one
192. 5-(4-Methoxy-naphthalen-1-ylmethyl)-thiazolidin-4-one
193. 5-(5-Methoxy-1*H*-indol-3-ylmethyl)-thiazolidin-4-one
194. 5-(4-Hydroxy-3,5-dimethoxy-benzyl)-thiazolidin-4-one
195. 5-(4-Isopropyl-benzyl)-thiazolidin-4-one
196. 5-(2-Methyl-3-phenyl-allyl)-thiazolidin-4-one
197. 5-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyl)-thiazolidin-4-one
198. 5-(2-Methyl-1*H*-indol-3-ylmethyl)-thiazolidin-4-one

199. 5-Benzofuran-2-ylmethyl-thiazolidin-4-one
200. 5-(4-Hexyl-benzyl)-thiazolidin-4-one
201 5-(3-Amino-benzyl)-thiazolidin-4-one
202 5-(3,5-Dimethyl-1-phenyl-1*H*-pyrazol-4-ylmethyl)-thiazolidin-4-one
203. 5-(2,2-Dimethyl-chroman-6-ylmethyl)-thiazolidin-4-one
204. 5-(4-Dibutylamino-benzyl)-thiazolidin-4-one
205. 5-(1-Hydroxy-naphthalen-2-ylmethyl)-thiazolidin-4-one
206. 5-(4-Octadecyloxy-benzyl)-thiazolidin-4-one
207. 5-(4-Methanesulphonyl-benzyl)-thiazolidin-4-one
208. 5-(2,6,6-Trimethyl-cyclohex-1-enylmethyl)-thiazolidin-4-one
209. 5-(1*H*-Pyrrol-2-ylmethyl)-thiazolidin-4-one
210. 5-(1-Methyl-1*H*-pyrrol-3-ylmethyl)-thiazolidin-4-one
211. 5-[4-(Benzo[1,3]dioxol-5-ylmethoxy)-benzyl]-thiazolidin-4-one

211. 2-Hydroxy-5-(4-oxo-thiazolidin-5-ylmethyl)-benzoic acid
212. 2-Hydroxy-5-(4-oxo-thiazolidin-5-ylmethyl)-benzoic acid
213. 5-(5,7-Dimethyl-4-oxo-4*H*-chromen-3-ylmethyl)-thiazolidin-4-one
214. 5-(6,8-Dimethyl-4-oxo-4*H*-chromen-3-ylmethyl)-thiazolidin-4-one
215. 5-(1-Phenyl-ethyl)-thiazolidin-4-one
216. 5-(1-Thiophen-2-yl-ethyl)-thiazolidin-4-one

The following Examples show some process variants which can be used for the synthesis of the compounds in accordance with the invention. However, they are not intended to be a limitation of the object of the invention. The structure of the compounds was proven by ^{1}H- and, where necessary, by ^{13}C-NMR spectroscopy. The purity of the substances was determined by C, H, N, P analysis as well as by thin-layer chromatography.

Example 1

General Process A:

A solution of 5 mmol of aldehyde R-CHO, wherein R has the given significance, or of the corresponding ketone and 5 mmol of 2-thioxo-thiazolidin-4-one in 30 ml of abs. toluene is treated with catalytic amounts of piperidinium acetate and heated at reflux

for 5 to 10 hours. Thereafer, the mixture is cooled to 0°C. The precipitate is filtered off under suction, rinsed with diethyl ether and dried.

5-(4-Bromo-benzylidene)-2-thioxo-thiazolidin-4-one (1)
M.p. 226-7°C

5-Naphthalen-2-ylmethylene-2-thioxo-thiazolidin-4-one (2)
Orange-red crystals; m.p. 268-70°C

5-Thiophen-3-ylmethylene-2-thioxo-thiazolidin-4-one (3)
M.p.. 204°C (dec.)

5-(4-Hydroxy-benzylidene)-2-thioxo-thiazolidin-4-one (4)
Yellow crystals; m.p.. 214-6°C

5-(3,4-Diethoxy-benzylidene)-2-thioxo-thiazolidin-4-one (5)
Yellow-orange crystals; m.p. 186-7°C

5-[3-(5,6-Diethoxy-benzo[b]thiophen-2-yl)-allylidene]-2-thioxo-thiazolidin-4-one (6)
Brown crystals; m.p. 268°C

5-Thiophen-2-ylmethylene-2-thioxo-thiazolidin-4-one (7)
Yellow crystals; m.p. 223-5°C

5-Furan-2-ylmethylene-2-thioxo-thiazolidin-4-one (8)
Orange crystals; m.p. 231-33°C

5-[3-(3,4-Diethoxy-2,5-dimethyl-phenyl)-allylidene]-2-thioxo-thiazolidin-4-one (9)
Brown crystals; m.p. 205-10°C

5-[1-(4-Chloro-phenyl)-ethylidene]-2-thioxo-thiazolidin-4-one (10)
Yellow crystals; m.p. 196-8°C

5-Pyridin-2-ylmethylene-2-thioxo-thiazolidin-4-one (11)
Olive green crystals; m.p. 250-5°C

5-(1-Phenyl-ethylidene)-2-thioxo-thiazolidin-4-one (12)
Yellow crystals; m.p. 166-8°C

5-(1-Thiophen-2-yl-ethylidene)-2-thioxo-thiazolidin-4-one (13)
Orange crystals; m.p. 218-20°C

5-(2-Hydroxy-benzylidene)-2-thioxo-thiazolidin-4-one (14)
M.p. 218°C (dec.)

5-(3,4-Dimethoxy-benzylidene)-2-thioxo-thiazolidin-4-one (15)
M.p. 187-9°C

5-(4-Isopropyl-benzylidene)-2-thioxo-thiazolidin-4-one (16)
M.p. 146-8°C

5-Naphthalen-1-ylmethylene-2-thioxo-thiazolidin-4-one (17)
M.p. 220-2°C

5-(5-Methyl-furan-2-ylmethylene)-2-thioxo-thiazolidin-4-one (18)
M.p. 227°C (dec.)

5-(4-Methoxy-benzylidene)-2-thioxo-thiazolidin-4-one (19)
M.p. 206°C (dec.)

5-(4-Ethoxy-benzylidene)-2-thioxo-thiazolidin-4-one (20)
M.p. 187-9°C

5-[3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-allylidene]-2-thioxo-thiazolidin-4-one (21)
Orange crystals; m.p. 205-10°C

5-(3-Benzo[b]thiophen-2-yl-allylidene)-2-thioxo-thiazolidin-4-one (22)
Orange crystals; m.p. 250°C

5-(3-Thiophen-2-yl-allylidene)-2-thioxo-thiazolidin-4-one (23)
Red-brown crystals; m.p. 213-6°C

5-(3-Naphthalen-2-yl-allylidene)-2-thioxo-thiazolidin-4-one (24)
Orange crystals; m.p. 256-8°C

5-[1-Methyl-3-(2,6,6-trimethyl-cyclohex-1-enyl)-allylidene]-2-thioxo-thiazolidin-4-one (25)
Yellow crystals; m.p. 189-10°C

5-(2-[1,3]Dioxolan-2-yl-6-fluoro-benzylidene)-2-thioxo-thiazolidin-4-one (26)
Beige crystals; m.p. 188-9°C

2-Thioxo-5-(2,6,6-trimethyl-cyclohex-1-enylmethylen)-thiazolidin-4-one (27)
Yellow crystals; m.p. 129-30°C

5-(4-Benzyl-benzylidene)-2-thioxo-thiazolidin-4-one (28)
Yellow-orange crystals; m.p. 210°C

5-(5,6-Diethoxy-benzo[b]thiophen-2-ylmethylene)-2-thioxo-thiazolidin-4-one (29)
Orange crystals; m.p. >250°C

5-[5-(5,6-Diethoxy-benzo[b]thiophen-2-yl)-penta-2,4-dienylidene]-2-thioxo-thiazolidin-4-one (30)
Dark brown crystals; m.p. 235-7°C

2-Thioxo-5-(1-p-tolyl-ethylidene)-thiazolidin-4-one (31)
Yellow crystals; m.p. 170-2°C

5-[1-(4-Methoxy-phenyl)-ethylidene]-2-thioxo-thiazolidin-4-one (32)
Yellow crystals; m.p. 164-6°C

5-[1-(3,4-Dichloro-phenyl)-ethylidene]-2-thioxo-thiazolidin-4-one (33)
Yellow crystals; m.p. 140-2°C

4-[4-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-benzyloxy]-benzonitrile (34)
Orange-brown crystals; m.p. 249-52°C

4-[4-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-butyric acid (35)
Orange-brown crystals; m.p. 201-2°C

5-(11-Oxo-6,11-dihydro-dibenzo[b,e]oxepin-3-ylmethylene)-2-thioxo-thiazolidin-4-one (36)
Brown crystals; m.p. 270-2°C

5-(1H-Imidazol-2-ylmethylene)-2-thioxo-thiazolidin-4-one (37)
Orange-red crystals; m.p. 256°C

5-Benzo[b]thiophen-2-ylmethylene-2-thioxo-thiazolidin-4-one (38)
Yellow-orange crystals; m.p. 277-80°C

5-[3-Methyl-5-(2,6,6-trimethyl-cyclohex-1-enyl)-penta-2,4-dienylidene]-2-thioxo-thiazolidin-4-one (39)
Red crystals; m.p. 170-3°C

5-(3,5-Di-tert-butyl-4-hydroxy-benzyliden)-2-thioxo-thiazolidin-4-one (40)
Yellow crystals; m.p. 244-6°C

5-Benzylidene-2-thioxo-thiazolidin-4-one (41)
Yellow crystals; m.p. 202°C

5-(1H-Pyrrol-2-ylmethylene)-2-thioxo-thiazolidin-4-one (42)
LSM-0042541 BM 17.0564 17 AF 0090/1
Orange-red crystals; m.p. 272-4°C

5-(1-Methyl-1H-pyrrol-2-ylmethylene)-2-thioxo-thiazolidin-4-one (43)
Red-brown crystals; m.p. 248-50°C

Ethyl 2-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-pyrrole-1-carboxylate (44)
Yellow crystals; m.p. 210-11°C

5-(4-Chloro-benzylidene)-2-thioxo-thiazolidin-4-one 5)
Yellow-orange crystals; m.p. 223-4°C

5-(3,4-Dichloro-benzylidene)-2-thioxo-thiazolidin-4-one (46)

Yellow-orange crystals; m.p. 234-5°C

Example 2

General Process B:

1.6 mmol of 2,6-dimethyl-1,4-dihydro-3,5-pyridinedicarboxylic acid ethyl ester are added to a suspension of 1.2 mmol of 2-thioxo-thiazolidin-4-one derivative (Example 1) in 20 ml of toluene. The mixture is heated to 80°C for 22 hours, then the solution is filtered while warm. The residue is rinsed with ethyl acetate. The combined org. phases are concentrated, taken up in ethyl acetate and extracted with 1M HCl, dried over sodium sulphate and concentrated.

Example 3

General Process C:

5 mmol of zinc dust in glacial acetic acid (5 ml/g zinc) are added to 1 mmol of rhodanine derivative (Example 2) divided into five portions in 30-60 minutes. Thereafter, the mixture is boiled at reflux for 2 to 24 hours. It is cooled to RT, infusorial earth is added and filtered off. The filtrate is treated with aqueous HCl and extracted with ethyl acetate. The combined org. phases are dried over sodium sulphate and concentrated. The residue is purified by chromatography (silica gel) with ethyl acetate/heptane.

Example 4

General Process D:

1 mmol of rhodanine derivative (Example 1) is dissolved in 40 ml of dioxan, treated with 1 mmol of P_2S_5 and heated at reflux. After 2 to 10 hours the mixture is treated with active charcoal and filtered. The dioxan is removed under a vacuum and the residue is

crystallized with ethanol. For purification, it is treated with cold dimethylformamide, treated with active charcoal and precipitated with water.

General Process E:

10 mmol of thiazolidine-2,4-dione (Chem. Heterocycl. Compds. EN 2_267-70, 1966) are stirred with 10 mmol of RCHO, in which R has the given significance, in 20 ml of methanol at room temperature for 60 min. The precipitate is filtered off under suction and recrystallized.

5-Naphthalen-1-ylmethylene-thiazolidine-2,4-dithione (47)
Red-brown crystals; m.p. 203°C (dec.)

5-Benzo[1,3]dioxol-5-ylmethylene-thiazolidine-2,4-dithione (48)
Red-brown crystals; m.p. 232°C (dec.)

5-(3-Benzo[b]thiophen-2-yl-allylidene)-thiazolidine-2,4-dithione (49)
Black crystals; m.p. 202-3°C

Example 5

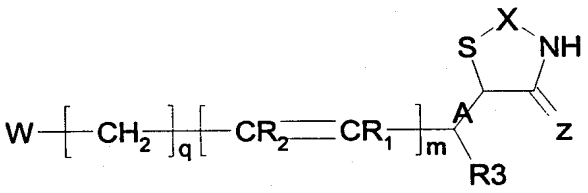
Compounds of general formula (I) are investigated in a suitable assay for the capability of stimulating cyclic adenylate cyclase.

Table I:

Example No.	Name	% cAMP (Test conc.50µM)
6	5-[3-(5,6-Diethoxy-benzo[b]thiophen-2-yl)-allylidene]-2-thioxo-thiazolidin-4-one	8
24	5-(3-Naphthalen-2-yl-allyliden)-2-thioxo-thiazolidin-4-on	8
25	5-[1-Methyl-3-(2,6,6-trimethyl-cyclohex-1-enyl)-allylidene]-2-thioxo-thiazolidin-4-one	8
27	2-Thioxo-5-(2,6,6-trimethyl-cyclohex-1-enylmethylene)-thiazolidin-4-one	10
39	5-[3-Methyl-5-(2,6,6-trimethyl-cyclohex-1-enyl)-penta-2,4-dienylidene]-2-thioxo-thiazolidin-4-one	8
40	5-(3,5-Di-tert-butyl-4-hydroxy-benzylidene)-2-thioxo-thiazolidin-4-one	15
49	5-(3-Benzo[b]thiophen-2-yl-allylidene)-thiazolidine-2,4-dithione	10

Patent Claims

1. Use of compounds of general formula (I)



(I)

in which

m signifies a number between 0 and 8,

q signifies a number between 0 and 8

X signifies the group CH_2 or C=S, whereby A signifies a single bond and m signifies 0 when X signifies CH_2,

A signifies a single or double bond

R_1, R_2 signify hydrogen or lower alkyl, whereby R_1 and R_2 can be the same or different and, when m signifies 2-8, R_1 and R_2 in the group $CR_1=CR_2$ can have various significances within the following sequence

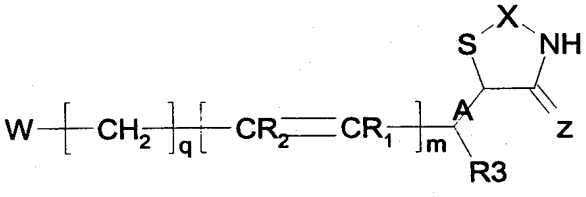
R_3 signifies hydrogen or lower alkyl

Z signifies oxygen, sulphur

W signifies an optionally mono- or polysubstituted saturated or unsaturated mono-, bi- or tricycle which can contain one or more hetero atoms,

for the preparation of medicaments for the treatment and prevention of metabolic bone disorders.

2. Compounds of general formula (I)



(I)

in which

m signifies a number between 0 and 8,

q signifies a number between 0 and 8

X signifies the group CH_2 or C=S, whereby A signifies a single bond and m signifies 0 when X signifies CH_2,

A signifies a single or double bond

R_1, R_2 signify hydrogen or lower alkyl, whereby R_1 and R_2 can be the same or different and, when m signifies 2-8, R_1 and R_2 in the group $CR_1=CR_2$ can have various significances within the following sequence

R_3 signifies hydrogen or lower alkyl

Z signifies oxygen, sulphur

W signifies an optionally mono- or polysubstituted saturated or unsaturated mono-, bi- or tricycle which can contain one or more hetero atoms,

whereas W is not phenyl, naphthyl, indolyl and thienyl, if X is C =S, Z is oxygen and m and q are both 0,

whereas W is not phenyl, furyl, thienyl and pyrrolyl, if X is C=S, Z is oxygen, A is a double bond and m is 0 or 1 and q is unequal 0 or m is unequal 0 and q is 2,

whereas W is not indolyl, if X is=S, Z is oxygen, A is a double bond and m is 1 and 1 is 0,

whereas W is not 4-(2,5-di-tert. butyl-phenol), if X is methylene,.

as well as their physiologically compatble salts, esters, optically active forms, racemates, tautomers, as well as derivatives which can be metabolized *in vivo* to compounds of general formula (I).

3. Medicament containing at least one compound of general formula (I) accordingly to claim 2 in admixture with usual pharmaceutical adjuvents and carrier materials

INTERNATIONAL SEARCH REPORT

Interi nal Application No
PCT/EP 99/07250

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/36 C07D277/34 A61K31/425 C07D417/06 C07D417/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 783 888 A (SANKYO COMPANY LIMITED) 16 July 1997 (1997-07-16) the whole document ---	1-3
X	EP 0 677 517 A (ELI LILLY AND COMPANY) 18 October 1995 (1995-10-18) cited in the application claims ---	1,2
X	EP 0 604 983 A (MITSUBISHI KASEI CORPORATION) 6 July 1994 (1994-07-06) claims ---	1,2
X	EP 0 587 377 A (ELI LILLY AND COMPANY) 16 March 1994 (1994-03-16) claims --- -/--	1,2

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 January 2000	14/01/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Henry, J

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INTERNATIONAL SEARCH REPORT

Interr. nal Application No
PCT/EP 99/07250

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 434 394 A (ELI LILLY AND COMPANY) 26 June 1991 (1991-06-26) claims	1,2
X	EP 0 398 179 A (NISSHIN FLOUR MILLING CO) 22 November 1990 (1990-11-22) cited in the application claims	1,2
X	EP 0 391 644 A (ELI LILLY AND COMPANY) 10 October 1990 (1990-10-10) claims	1,2
X	EP 0 343 643 A (WARNER- LAMBERT COMPANY) 29 November 1989 (1989-11-29) claims	1,2
X	EP 0 316 790 A (NISSHIN FLOUR MILLING CO) 24 May 1989 (1989-05-24) claims	1,2
X	EP 0 237 138 A (YAMANOUCHI PHARMACEUTICAL CO LTD) 16 September 1987 (1987-09-16) claims	1,2
X	EP 0 211 670 A (ELI LILLY AND COMPANY) 25 February 1987 (1987-02-25) cited in the application claims	1,2
X	WO 98 01445 A (SMITHKLINE BEECHAM S.P.A.) 15 January 1998 (1998-01-15) cited in the application claims	1-3
X	WO 96 26207 A (NISSAN CHEMICAL INDUSTRIES LTD) 29 August 1996 (1996-08-29) cited in the application claims	1,2
X	FR 2 196 797 A (ARIES ROBERT) 22 March 1974 (1974-03-22) the whole document	1,2
X	US 5 747 517 A (PANETTA JILL A.) 5 May 1998 (1998-05-05) claims	1,2

-/--

1

INTERNATIONAL SEARCH REPORT

Intern. ıal Application No
PCT/EP 99/07250

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate. of the relevant passages	Relevant to claim No.
X	HANS BEHRINGER ET AL: "Substituierte 5-methylen-rhodanine aus 5-chlormethylen-rhodaninen" CHEMISCHE BERICHTE., vol. 91, 1958, pages 2773-2782, XP002093301 WEINHEIM DE *pages 2773,2774,2779 ---	1
X	P.M. CHAKRABARTI ET AL: "An improved synthesis of substituted benzo'b!thiophen-2-carboxylic acids and related acids" TETRAHEDRON., vol. 25, 1969, pages 2781-2785, XP002093302 OXFORD GB page 2782 -page 2783 ---	1
X	CHEMICAL ABSTRACTS, vol. 120, no. 17, 25 April 1994 (1994-04-25) Columbus, Ohio, US; abstract no. 208602b, YASUHIRO O: page 101; XP002093303 abstract & JP 05 306224 A (WAKAMOTO PHARMA CO.LTD) 19 November 1993 (1993-11-19) ---	1,2
A	EP 0 691 129 A (ELI LILLY AND COMPANY) 10 January 1996 (1996-01-10) claims -----	1-3

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/07250

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 2 PARTIALLY
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 2 PARTIALLY

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of claim 2(compounds per se) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). Consequently, the search report with regard to said claim has been limited to a selection of retrieved novelty-affecting documents with special emphasis to the componds illustrated by the examples and the list of prefered compounds of pages 10-16.
It should however be noted that the search and the search report can be considered as covering all claimed compounds of the prior art insofar those display an activity for the treatment and the prevention of metabolic bone disorders

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter... nal Application No
PCT/EP 99/07250

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0783888 A	16-07-1997	AU 7650396 A	03-07-1997
		CA 2193751 A	27-06-1997
		CZ 9603827 A	16-07-1997
		HU 9603607 A	28-07-1998
		JP 9235229 A	09-09-1997
		NO 965563 A	27-06-1997
		US 5804590 A	08-09-1998
EP 0677517 A	18-10-1995	CA 2144385 A	17-09-1995
		JP 7258235 A	09-10-1995
		US 5747517 A	05-05-1998
EP 0604983 A	06-07-1994	AT 145400 T	15-12-1996
		CA 2112331 A	29-06-1994
		DE 69306094 D	02-01-1997
		DE 69306094 T	03-04-1997
		DK 604983 T	09-12-1996
		ES 2097431 T	01-04-1997
		GR 3021746 T	28-02-1997
		JP 2845743 B	13-01-1999
		JP 6247945 A	06-09-1994
		US 5594016 A	14-01-1997
EP 0587377 A	16-03-1994	AU 676843 B	27-03-1997
		AU 4621893 A	17-03-1994
		CA 2105598 A	11-03-1994
		CN 1091006 A	24-08-1994
		CZ 9301814 A	16-03-1994
		EP 0915090 A	12-05-1999
		FI 933946 A	11-03-1994
		HU 70184 A	28-09-1995
		IL 106877 A	10-03-1998
		IL 119119 A	16-08-1998
		JP 6192091 A	12-07-1994
		MX 9305444 A	31-05-1994
		NO 933198 A	11-03-1994
		NO 981911 A	11-03-1994
		NZ 248573 A	27-02-1996
		PL 300335 A	21-03-1994
		US 5523314 A	04-06-1996
		US 5716975 A	10-02-1998
		US 5661168 A	26-08-1997
		ZA 9306492 A	02-03-1995
EP 0434394 A	26-06-1991	AT 169294 T	15-08-1998
		AU 639734 B	05-08-1993
		AU 6826690 A	27-06-1991
		CA 2032330 A	22-06-1991
		CN 1052668 A,B	03-07-1991
		DE 69032537 D	10-09-1998
		DE 69032537 T	21-01-1999
		ES 2121748 T	16-12-1998
		FI 906273 A	22-06-1991
		HU 216732 B	30-08-1999
		IL 96654 A	29-06-1995
		IL 108962 A	05-12-1996
		JP 4279573 A	05-10-1992
		MX 23803 A	28-02-1994

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter: nal Application No
PCT/EP 99/07250

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0434394 A		NO 300458 B	02-06-1997
		NZ 236472 A	26-03-1993
		PT 96198 A,B	30-09-1991
		RU 2036915 C	09-06-1995
		RU 2050355 C	20-12-1995
		US 5387690 A	07-02-1995
		US 5216002 A	01-06-1993
EP 0398179 A	22-11-1990	DE 69024843 D	29-02-1996
		DE 69024843 T	30-05-1996
		KR 9608245 B	21-06-1996
		US 5116855 A	26-05-1992
		CA 2016665 A	19-11-1990
		JP 3072471 A	27-03-1991
EP 0391644 A	10-10-1990	AT 139531 T	15-07-1996
		AU 629322 B	01-10-1992
		AU 5293490 A	11-10-1990
		CA 2013599 A	07-10-1990
		DE 69027472 D	25-07-1996
		DE 69027472 T	05-12-1996
		DK 391644 T	15-07-1996
		ES 2088965 T	01-10-1996
		GR 3020500 T	31-10-1996
		JP 2290862 A	30-11-1990
		US 5356917 A	18-10-1994
		US 5691367 A	25-11-1997
EP 0343643 A	29-11-1989	AT 103175 T	15-04-1994
		AU 626863 B	13-08-1992
		AU 3505889 A	30-11-1989
		CA 1340247 A	15-12-1998
		DE 68914029 D	28-04-1994
		DE 68914029 T	07-07-1994
		DK 252089 A	26-11-1989
		EP 0565135 A	13-10-1993
		ES 2063073 T	01-01-1995
		FI 892522 A	26-11-1989
		IE 62214 B	11-01-1995
		JP 2062864 A	02-03-1990
		JP 2899309 B	02-06-1999
		KR 9702228 B	26-02-1997
		NO 892083 A	27-11-1989
		NZ 229266 A	23-12-1991
		PH 27092 A	26-02-1993
		PT 90662 A,B	30-11-1989
		US 5464856 A	07-11-1995
		US 5208250 A	04-05-1993
		US 5306822 A	26-04-1994
EP 0316790 A	24-05-1989	CA 1336837 A	29-08-1995
		DE 3883164 A	16-09-1993
		DE 3883164 T	02-12-1993
		ES 2059471 T	16-11-1994
		JP 1230565 A	14-09-1989
		JP 2645114 B	25-08-1997
		KR 9609424 B	19-07-1996
		US 4897406 A	30-01-1990

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ...nal Application No
PCT/EP 99/07250

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 0237138	A	16-09-1987	AU	6740187 A	09-07-1987
			DK	4487 A	08-07-1987
			JP	63165368 A	08-07-1988
EP 0211670	A	25-02-1987	AT	52412 T	15-05-1990
			AU	590312 B	02-11-1989
			AU	6097286 A	12-02-1987
			CA	1285572 A	02-07-1991
			CN	1014891 B	27-11-1991
			CY	1619 A	10-07-1992
			DK	376986 A	10-02-1987
			ES	2001075 A	16-04-1988
			GR	862081 A	24-12-1986
			HK	94791 A	29-11-1991
			HU	42765 A	28-08-1987
			IE	58718 B	03-11-1993
			IL	79648 A	12-12-1991
			JP	1902370 C	08-02-1995
			JP	6025182 B	06-04-1994
			JP	62042977 A	24-02-1987
			KR	8700889 B	02-05-1987
			LV	10866 A	20-10-1995
			LV	10866 B	20-04-1996
			MX	9203108 A	01-07-1992
			NZ	217126 A	27-01-1989
			PH	24517 A	18-07-1990
			PT	83152 A,B	01-09-1986
			SG	80391 G	15-11-1991
			SU	1516012 A	15-10-1989
			RU	2014329 C	15-06-1994
			US	5356917 A	18-10-1994
			US	5691367 A	25-11-1997
WO 9801445	A	15-01-1998	EP	0912560 A	06-05-1999
			US	5985905 A	16-11-1999
WO 9626207	A	29-08-1996	AU	4731196 A	11-09-1996
			JP	9235284 A	09-09-1997
			ZA	9601478 A	28-08-1996
FR 2196797	A	22-03-1974	NONE		
US 5747517	A	05-05-1998	CA	2144385 A	17-09-1995
			EP	0677517 A	18-10-1995
			JP	7258235 A	09-10-1995
JP 05306224	A	19-11-1993	NONE		
EP 691129	A	10-01-1996	US	5476865 A	19-12-1995
			CA	2153213 A	07-01-1996
			JP	8040897 A	13-02-1996